REVIEW ARTICLE

TREATMENT OF SEVERE AORTIC STENOSIS IN PATIENTS WITH LOW SURGICAL RISK

ABSTRACT

Following the first implantation of a percutaneous valve in 2002, two of the leading manufacturers of biological valve prostheses developed percutaneous aortic platforms, which have promoted transcatheter aortic valve implantation (TAVI) as an alternative to surgical aortic valve replacement (SAVR). In the last decade, both companies have funded six randomized studies grouping patients according to surgical risk and comparing the results between the two therapies. None of these studies has demonstrated the superiority of one technique over the other in terms of 5-year mortality. In general, patients who received percutaneous valves suffered a higher incidence of the need for pacemaker implantation, perivalvular leaks, and vascular complications, while surgical patients suffered more bleeding and atrial fibrillation. Following these results, the use of TAVI in young and low-risk patients has exponentially increased.

Keywords: *percutaneous valves, transcatheter aortic valve implantation, surgical aortic valve replacement.*

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INTRODUCTION

On April 16, 2022, Dr. Alain Cribier[1] implanted the first percutaneous valve in the aortic position as a last therapeutic resort for a 57-year-old man with severe calcific aortic stenosis (AS). Several teams of cardiovascular surgery professionals had rejected aortic valve replacement because of his hemodynamic instability and significant comorbidities. A marked clinical improvement was observed in the first 48 hours after implantation, with reduced signs of congestive heart failure. During the subsequent 4 months, several non-cardiac complications appeared: a) an episode of pulmonary embolism on day 3, which required intravenous fibrinolysis; b) an episode of septicemia on day 10 with septic shock; and c) a progressive worsening of the previous ischemia of the right lower limb, which required supracondylar amputation 10 weeks after implantation of the percutaneous prosthesis. The patient's clinical condition progressively deteriorated, leading to death 17 weeks after prosthesis implantation[2].

Following this episode, two leading manufacturers of biological valve prostheses, Edwards Lifesciences (Irvine, California, United States of America [USA]) and Medtronic Inc (Minneapolis, Minnesota, USA), each developed a percutaneous aortic stent platform, the Sapiens™, and the CoreValve™. These prostheses have spearheaded the establishment of transcatheter aortic valve implantation (TAVI) as an alternative to surgical aortic valve replacement (AVR).

In this regard, over the past two decades, the industry, supported by many interventional cardiologists, has tried to establish percutaneous treatment of aortic stenosis as the first choice in patients with severe aortic stenosis. To prove that percutaneous implantation of aortic prostheses is comparable to conventional surgery, both companies designed randomized studies in which they grouped patients according to surgical risk and compared the outcomes of patients who received percutaneous treatment and those who received surgical treatment.

TRIALS IN HIGH-RISK PATIENTS

The PARTNER 1A (Edwards Lifesciences Sapiens valve) and US Corevalve (Medtronic Inc. CoreValve) trials in high-risk surgical patients demonstrated promising results in the percutaneous prosthesis-treated groups.

In PARTNER 1A (mean age 84 years, mean Society of Thoracic Surgeons ([STS] score 11.7%), transcatheter and surgical procedures had similar survival and significant complication rates in the first year (except major bleeding, which was more frequent in patients treated with RQVA, and vascular complications, which were more frequent in the TAVI group)[3]. At 5 years, although survival in the surgical treatment group was higher than in the TAVI group, this difference was insignificant[4].

In the CoreValve US (mean age 83 years and STS score of 7.4%), the implantation of a self-expandable transcatheter aortic valve prosthesis was associated with a higher 1-year survival rate than that of RQVA[5]. At 5 years, the difference in survival rate had disappeared, and there were no significant differences in other variables, except major vascular complications or the need for permanent pacemaker implantation, which were higher in the TAVI group[6].

In summary, these two randomized trials in patients at high surgical risk showed no significant differences in survival or complications, except vascular complications or the need for pacemaker implantation at 5 years with the self-expanding prosthesis CoreValve™.

TRIALS IN INTERMEDIATE-RISK PATIENTS

Following the favorable results observed after one year in high-risk patients, the two manufacturers initiated trials in intermediate-risk patients, PARTNER 2 (Edwards Lifesciences) and SURTAVI (Medtronic Inc.).

In PARTNER 2 (mean age 81 years, mean STS score 5.8%), no significant differences were observed in the composite primary outcome of death or disabling stroke at 30 days, at 1 and 2 years. The only significant differences at 2 years were in life-threatening bleeding and atrial fibrillation, both more prevalent in the RQVA group, and vascular complications, more frequent in the TAVI group. In this study, there were no differences in the need for pacemaker implantation between the two types of treatment[7]. At 5 years, there were no significant differences in the incidence of death from any cause or disabling stroke between the TAVI group and the surgery group. More patients in the TAVI group than in the TAVR group had at least mild paravalvular aortic regurgitation. Hospital readmissions, such as aortic valve reoperations, were more frequent after TAVI than after surgery. The improvement in health status at 5 years was similar in both[8].

In SURTAVI (mean age 79 years, mean STS score 4.5%), 30-day, 1-year, and 2-year mortality were similar in the two groups. The TAVI group had a significantly higher rate than the RQVA group in terms of vascular complications, residual aortic

insufficiency, and need for pacemaker implantation; conversely, the RQVA group suffered more episodes of atrial fibrillation and renal failure and required more transfusions than the TAVI group, with statistically significant differences[9]. At 5 years, no differences were identified in the composite primary outcome of death or disabling stroke between the TAVI and RQVA groups. However, there were more valve-related reinterventions in the TAVI group. The rate of patients requiring pacemaker implantation was 39.1% in patients treated with percutaneous prosthesis[10].

These trials informed the recommendations of the 2017 European Society of Cardiology/European Association for Cardiothoracic Surgery (ESC/EACTS) guidelines on the management of valvular heart disease, in which RQVA was recommended for patients at low surgical risk and without other risk factors such as frailty, porcelain aorta, and sequelae of thoracic radiation. For patients with increased surgical risk (STS or EuroSCORE II ≥4% or logistic EuroSCORE I ≥10%) or with other risk factors such as those described above, the decision between RQVA and TAVI should be made by the cardiology team based on individual patient characteristics, with a preference for TAVI for older individuals with possible femoral access[11].

Before the publication of the 2017 European guidelines, a progressive increase in the use of TAVI had already been noticed, especially in patients older than 80 years[12-14].

TRIALS IN LOW-RISK PATIENTS

However, it was after the publication of the trials in low-risk patients PARTNER 3 (promoted by Edwards Lifesciences) and Evolut LR (promoted by Medtronic Inc.) and the subsequent approval by the Food and Drug Administration (FDA) of the use of TAVI in low-risk patients,[15] when an increase in the use of percutaneous prostheses for the treatment of severe aortic stenosis in younger patients was noted, with a consequent decrease in the RQVA in this group of patients[16].

Given the expansion of percutaneous aortic prostheses in patients with AS,[17] it is essential to deepen the methods and results of both trials, understand their limitations, and evaluate the consequences of the indiscriminate use of TAVI in young, low-risk patients.

PARTNER 3 and Evolut LR are noninferiority trials in which patients were randomized 1:1 to TAVI or RQVA. In PARTNER 3, 1000 patients with severe aortic AS and low surgical risk, with a mean STS score of 1.9%, were randomized to transfemoral TAVI with a SAPIEN balloon-expandable valve S3™ (Edward Lifesciences) or RQVA. The impossibility of implanting the percutaneous prosthesis via femoral access (which requires a minimum vessel diameter >5.0 mm for 14 Fr and >5.5 mm for 16 Fr) was an exclusion criterion[18].

On the other hand, in the Evolut LR, 1468 patients with severe AS and low surgical risk (mean STS score of 1.9%) were randomized to TAVI with a self-expandable valve Evolut™ (Medtronic Inc.) or RQVA. A total of 1403 patients underwent the assigned procedure. Almost all TAVI procedures were performed via the transfemoral route (99%)[19].

Patients enrolled in these trials were approximately a decade younger than participants in previous studies (mean age 73 years in PARTNER 3 and 74 years in Evolut LR). Similar primary and secondary outcome variables were established in both studies, providing an opportunity to extrapolate their findings to clinical practice.

In PARTNER 3[18], the primary endpoint was a composite of all-cause mortality, any stroke, and rehospitalization (prosthesis- or procedure-related, including heart failure) 1 year after the procedure. The secondary variables were as follows:

- New-onset atrial fibrillation at 30 days.
- Duration of index hospitalization.
- Death from any cause, any stroke, and rehospitalization at 1 year (primary variable: evidence of superiority).
- Death, Kansas City Cardiomyopathy Questionnaire (KCCQ) score <45 or KCCQ decline ≥10 points from baseline to 30 days.
- Death or stroke at 30 days.
- Stroke at 30 days.

Although the baseline characteristics of the patients were similar in both groups, it should be noted that 26.4% of patients in the group randomized to RQVA required an additional procedure (12.8% of the total underwent one or more coronary artery bypass grafts), whereas this was the case in only 7.9% in the TAVI group (6.5% underwent percutaneous coronary intervention).

At 1 year, the composite of death from any cause, stroke, or rehospitalization occurred in 42 patients (8.5%) in the TAVI group compared with 68 patients (15.1%). Noninferiority and superiority were met, with an absolute difference between the TAVI group and the surgery group of -6.6 percentage points (95% confidence interval [CI], -10.8 to -2.5; P<0.001 for noninferiority) and a hazard ratio of 0.54 (95% CI, 0.37 to 0.79; P=0.001 for superiority). Although there were no significant differences in death of any type and stroke between the two groups, there were

substantial differences in the composite variable of death and stroke and other variables, such as rehospitalization and life-threatening bleeding, always in favor of TAVI. In this study, there were no differences in vascular complications or the need for pacemaker implantation (although there were differences in the occurrence of left bundle branch block). The differences above were maintained concerning the primary composite variable and its components in the subgroup of patients in whom concomitant procedures were not performed.

At 1 year, the mean aortic valve gradient was 13.7 mm Hg in the TAVI group and 11.6 mm Hg in the surgical group. The mean aortic valve area was 1.7 cm^2 and 1.8 cm^2, respectively. Aortic annulus enlargement was performed in 4.6% of the patients in the TAVI group, and 20.1% of the total had a 19 or 21-mm prosthesis implanted. Fifty-one percent of the prostheses used were Magna Ease™ (Edwards Lifesciences), 8.2% were porcine prostheses, and 16.8% of the patients were implanted with prostheses that were almost obsolete or withdrawn from the market, such as the Trifecta™ (Abbott Vascular, Santa Clara, California, USA) or LivaNova Mitroflow™ and Crown™ (LivaNova, London, United Kingdom)[20]. The percentage of patients with moderate or severe paravalvular regurgitation did not differ significantly between the TAVI and the surgery groups (0.8% and none, respectively, at 30 days; 0.6% and 0.5% at 1 year). The percentage of patients with mild paravalvular regurgitation at 1 year was higher with TAVI than with surgery (29.4% vs. 2.1%). There were no episodes of valve thrombosis associated with clinical events, although 6 asymptomatic patients (5 in the TAVI group and 1 in the RQVA group) had findings suggestive of valve thrombosis[19].

In PARTNER 3, the results at 5 years were less advantageous for the TAVI group[20]. The superiority in the primary variable had disappeared. Concerning the number of deaths from any cause and stroke, both were more frequent in the TAVI group than in the surgical group, although without significant differences. The only variable that reached substantial differences in favor of RQVA was that of valvular thrombosis adjudicated according to VARC 3 criteria. At this point, it is essential to note that while, at hospital discharge, 45.8% of patients in the RQVA group and 21.2% of patients in the TAVI group were on treatment with anticoagulants, at 5 years, the rate was 24.9%, and 24.8%, respectively. Importantly, for the composite variable of death from any cause and disabling stroke, the risk ratio (RR) was 1.6 (95%CI: 1.00-2.55).

In the Evolut LR, the primary hypothesis was that the incidence of the primary endpoint (death from any cause or disabling stroke at 24 months) with TAVI is non-inferior to surgery, with a margin of 6%[21].

The following secondary objectives were tested in order, and testing continued if and only if all previous objectives had met the designated success criterion:

- Mean transvalvular gradient at 1 year (noninferiority).
- Effective orifice area at 1 year (noninferiority).
- Change in New York Heart Association (NYHA) classification from baseline to 1 year (noninferiority).
- Change in KCCQ score from baseline to 1 year (noninferiority).
- Mean transvalvular gradient at 1 year (superiority).
- Effective orifice area at 1 year (superiority).
- Change in KCCQ score from baseline to 30 days (superiority).

Additional secondary safety endpoints included:

- A composite of death, disabling stroke, life-threatening bleeding, major vascular complication, or stage 2 or 3 acute kidney injury at 30 days.
- Prosthetic valve endocarditis.
- Prosthetic valve thrombosis.
- Prosthetic valve dysfunction requiring a repeat procedure.
- Stroke.
- Life-threatening bleeding at 12 months.

Other procedures were performed in 26% of patients in the treatment group. For example, in this group, 92 (13.1%) patients received coronary artery bypass grafts, and 24 (3.5%) underwent surgical ablation of atrial fibrillation.

The incidence of death or disabling stroke at 24 months was 5.3% in the TAVI group and 6.7% in the surgery group. The prespecified criterion of noninferiority was met, but the prespecified criterion of superiority was not met.

Concerning the incidence of de novo atrial fibrillation at 30 days, it was found in 7.7% of patients in the TAVI group and 35.4% in the surgery group. In contrast, definitive pacemaker implantation was performed in 17.4% of patients in the TAVI group and 6.1% in the surgery group. Hospitalization for heart failure during the 12-month follow-up period occurred in 3.2% of patients in the TAVI group and 6.5% in the surgery group. The overall summary score (±DE) of the KCCQ measuring the quality of life was 88.7±14.2 in the TAVI group and 78.6±18.9

in the surgery group at 30 days, with no differences between groups observed at 12 months. Differences in the rest of the secondary variables were not statistically significant.

Although there is information on the size of the surgical prostheses used in Evolut LR (22% of patients received prostheses of size 19 or 21 mm), the type or manufacturer of the prostheses was not specified.

Four-year outcomes could be assessed in 94.7% of patients in the TAVI group and 89.2% of patients in whom AVR was indicated. The primary endpoint of all-cause mortality or disabling stroke at 4 years was 10.7% in the TAVI group and 14.1% in the SAVR group (RR: 0.74; 95%CI: 0.54-1.00; P = 0.05), representing a 26% relative reduction in the risk of death or disabling stroke with TAVI compared with RQVA. The absolute difference between treatment groups for the primary endpoint continued to increase over time: -1.8% at 1 year, -2.0% at 2 years, -2.9% at 3 years, and -3.4% at 4 years. Rehospitalization for heart failure was 10.3% with TAVI versus 12.1% in the RQVA group. The percentage of patients requiring new permanent pacemaker implantation was significantly higher in the TAVI group (24.6% vs. 9.9%; P <0.001). Reintervention on the aortic valve prosthesis, clinical or subclinical valve thrombosis, and prosthetic endocarditis were also low in both groups.

Regarding valve hemodynamics, TAVI patients had significantly lower mean aortic valve gradients (9.8±5.5 mmHg in the TAVI group versus 12.1±5.4 mmHg in the RQVA group; P<0.001) and a larger effective area (2.1±0.6 cm^2 in the TAVI group versus 2.0±0.6 cm^2 in the RQVA group; P <0.001). Although there were no differences in the incidence of moderate or severe paravalvular regurgitation, mild regurgitation was detected in 14.9% of patients in the TAVI group and 1.6% of those in the RQVA group[22].

In summary and concerning the two studies in low-risk patients, it can be said that in the medium term (5 years in the PARTNER 3 and 4 years in the Evolut LR), the differences in the outcome variables indicate that these were more positive for the Evolut prosthesis than the Sapiens 3 compared to the RQVA. This was observed for most variables, except the need for pacemaker implantation (*Table 1*).

Variable	PARTNER 3 (5 years)		EVOLUT LR (4 years)	
	TAVI	RQVA	TAVI	RQVA
Primary[a]	22.8%	27.2%	10.7%	14.1%
Death + incapacitating stroke	12.9%	10.9%	10.7%	14.1%
Rehospitalization	13.7%	17.4%	10.3%	12.1%
Need of pacemaker	13.5%	10.4%	24.6%	9.9%[b]
Mild paravalvular insufficiency	19.9%	3.2%[b]	14.9%	1.6%[b]
Valvular thrombosis	2.5%	0.2%[b]	0.7%	0.6%

TABLE 1. Comparison of results between the PARTNER 3 and EVOLUT LR trials
CVA: cerebrovascular accident; AVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation.
[a]Evolut LR: death from any cause or disabling stroke. PARTNER 3: All-cause mortality, any stroke, and rehospitalization.
[b]Significant difference.

Based on the above data, we conclude that, in the population studied, the mid-term results are similar between both techniques (TAVI and RQVA), with the only difference being the number of patients requiring permanent pacemaker implantation if treated with a Medtronic Evolut™ prosthesis. It is not surprising then that the FDA approved the use of TAVI in patients with low-risk patients and that the performance of percutaneous aortic valve implantation has grown almost exponentially in some countries. At the 60th Annual Congress of the US STS, data on the use of TAVI in California were presented, showing that nearly 50% of patients under 60 years of age choose TAVI over TAVR for treating AS[23].

STRUCTURAL DETERIORATION OF BIOLOGICAL PROSTHESES

This increasing trend in the use of percutaneous biological prosthesis implantation in patients with a life expectancy of more than 10 years will lead to a growing number of patients with degraded percutaneous prostheses requiring treatment.

Advances in materials biotechnology, transcatheter prosthesis designs, and tissue preservation and folding techniques promise to increase the durability of these

prostheses. However, it is also true that, although the anti-calcification treatments of conventional prostheses are similar to those used for percutaneous prostheses, in the latter, the manipulation required for valve folding and post-dilatation maneuvers can cause microtrauma at the level of the leaflets, which can contribute to prosthetic degeneration[24,25].

In a study with finite element analysis in a computational model of soft tissue fatigue damage, investigating the fatigue of surgical and percutaneous prosthesis leaflets, it was observed that percutaneous prosthesis leaflets suffer more significant stress, deformation, and fatigue damage compared to surgical prosthesis leaflets. Simulation results suggest that the durability of percutaneous prostheses can be significantly reduced compared to surgical prostheses to 7.8 years[26].

Beyond the technical peculiarities of prosthesis manipulation during implantation, and far from the non-touch approach used with conventional surgical prostheses, it should be considered that the permanence of the native aortic valve increases perivalvular turbulent flows, which is likely to accelerate the degeneration process[27,28].

Subclinical leaflet thrombosis, defined as hypoattenuating thickening on cardiac tomography appears more frequently in patients who have undergone TAVI than in those treated with TAVI[29]. This phenomenon may be related to the stagnation of blood flow in the aortic root after percutaneous valve implantation[30].

In the PARTNER 3 4D cardiac computed tomography (CT) substudy, 435 patients with severe AS and low surgical risk were randomized to TAVI (n = 214) versus TAVI (n = 221) and underwent 4D cardiac CT at 30 days and 1 year after surgery. Subclinical thrombosis at 30 days was significantly more frequent in patients treated with TAVI (13% vs. 5%, P = 0.03), although this difference disappeared at 1 year[31].

Although a causal relationship between subclinical thrombosis and altered valve hemodynamics or thromboembolic risk has not been demonstrated, analysis of 890 patients included in the Registry for Evaluation of Transcatheter and Surgical Aortic Bioprosthetic Aortic Valve Thrombosis and Anticoagulation Therapy (RESOLVE, (RESOLVE) registry) and of 264 patients included in the registry of subclinical aortic bioprosthetic valve thrombosis evaluated with 4-dimensional computed tomography (SAVORY) who had 4D cardiac CT, has shown a significant increase in the incidence of transient cerebral ischemic attacks as well as a higher proportion of increased valve gradients in patients with subclinical thrombosis. Thus, Subclinical thrombosis represents valvular dysfunction and may progress to impaired leaflet motion[32,33].

The long-term clinical impact of this phenomenon is unknown. There is insufficient evidence on its implications in young patients: the increased risk of prosthetic degeneration in young people is a well-documented phenomenon in TAVI, and although there is no comparable evidence for the TAVI population, it can be expected to represent a potential problem in the long term. Furthermore, as has been the case with some prosthetic valves used in TAVI and subsequently withdrawn from the market, it is expected that some transcatheter bioprostheses' durability may be disappointing at follow-up.

When percutaneous treatment is considered in the low-risk population, which is therefore also eligible for AVR, a reflection on the durability and results of the treatment offered is mandatory.

EXPLANTATION OF PERCUTANEOUS PROSTHESES

The increasing choice of using biological valves by transcatheter implantation, as has occurred in conventional surgery, implies the assumption that patients are likely to require more than one intervention on the aortic valve during the patient's lifetime. It is to be expected that percutaneous prosthesis explantation surgery will experience an exponential increase in demand in the coming years[34].

In the EXPLANT-TAVR, an international multicenter retrospective registry including 269 patients who underwent transcatheter prosthesis explantation, 43.1% of patients required the intervention due to the development of endocarditis. Other causes of explantation were prosthetic degeneration (20.1%), perivalvular leak (18.2%), and prosthesis-patient mismatch (10.8%). The results reveal a non-negligible risk associated with explant surgery, with in-hospital, 30-day, and 1-year mortality of 11.9%, 13.1%, and 28.5%, respectively[35].

Explanting a percutaneous prosthesis is a surgery that can have complications; it is often associated with urgent or emergencies (53.1% of the patients included in the EXPLANT-TAVR) and can require extensive endarterectomies due to neoendothelialization of the prostheses.

In the EXPLANT-TAVR registry, the mortality of surgical explant of a transcatheter prosthesis had high mortality (13.6%) at 30 days, compared to the mortality in the TAVI-in-TAVI group, which was 3.6%. This difference was still significant at 1 year (32.4% vs. 15.4%). However, the difference in mortality after 30 days was not significant[36].

The alternative to the surgical explant of a percutaneous prosthesis is the implantation of a second transcatheter prosthesis. The "valve-in-valve" or "TAVI-in-TAVI" techniques are under development and do not currently represent a safe and viable solution in all patients, especially when the cause of reintervention is of infectious etiology or when the size of the implanted prostheses is small. Moreover, there are compelling reasons to doubt the possibility of applying this strategy in a generalized manner.

The so-called sequestration of the sinuses of Valsalva by the prostheses can obstruct the coronary ostia and make their cannulation almost impossible for percutaneous coronary procedures should these be necessary in the future[37,38]. The absence of data on the incidence of thrombosis or patient-prosthesis mismatch in patients with TAVI-in-TAVI precludes recommending this technique to support a TAVI treatment strategy in patients with a life expectancy of more than 10 years.

The development of TAVI is a revolutionary event in our milieu and opens the doors of AS treatment for patients with high surgical risk who lack options. However, the growing use of the transcatheter option and the continuous development of implantation techniques mean that the therapeutic plan will be increasingly individualized shortly.

The long-term approach must consider comorbidities, anatomy, and the relative advantages and disadvantages of the two therapies, not only about the index surgery but also all possible combination scenarios of the two treatments throughout the patient's lifetime.

Therefore, in low-risk patients, TAVI should be the option of choice only for those with a life expectancy of less than 10 years. In the remainder, TAVI is the safest long-term alternative.

Declarations

The authors declare no conflict of interest.

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